ABSTRACT

Topiramate has been under investigation for the past several years as a prophylactic agent for migraine and other headache disorders. Studies to date have shown it to be safe and effective. As with other antiepileptic drugs, its exact mechanisms of action are not yet known, or at least, the mechanisms that are important in its efficacy in migraine are not yet defined. Topiramate acts on several receptors and ion channels as well as neurotransmitter metabolism. As a result, it inhibits excitatory neurotransmission through several mechanisms. This article briefly reviews the rationale for using antiepileptic drugs in migraine and offers results of a recent study of topiramate as migraine prophylaxis in 213 patients. The results support earlier studies that topiramate is safe and effective. Based on the data reported here, the agent appears to have particular benefit for those suffering from migraine with aura.

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PROCEEDINGS

EFFICACY OF TOPIRAMATE IN MIGRAINE PROPHYLAXIS: A RANDOMIZED CONTROLLED STUDY*

Based on a presentation by Stephen D. Silberstein, MD†

*This article is based on a presentation given by Dr. Silberstein at the 44th Annual Meeting of the American Headache Society.
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CACNA1A was the first gene to be identified as being involved in familial hemiplegic migraine, a rare subtype of migraine, and may be involved in migraine with aura as well. Located on chromosome 19, it encodes the alpha-1A subunit of a voltage-dependent calcium channel. CACNA1A is found in patients with familial hemiplegic migraine and episodic ataxia, another disorder with intermittent presentation in otherwise healthy individuals. Long-QT syndrome is a cardiac arrhythmia resulting from mutations in either voltage-gated sodium or potassium channels. Collectively, these types of diseases—episodic in otherwise healthy people with known mutations in ion channels—are collectively referred to as channelopathies. They all respond to similar drug classes and share common precipitating factors.

Gamma-aminobutyric acid (GABA) and glutamate are also of great interest in migraine pathophysiology. Topiramate appears to activate GABA receptors (type A), inhibiting glutamate excitatory transmission. Glutamate may also be a player in migraine onset; several investigators have discovered increased plasma and cerebrospinal fluid levels of glutamate, which increase even further during a migraine attack, but the results sometimes vary. Glutamate binds to N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)/kainate receptors. Topiramate deactivates AMPA/kainate receptors, thus blocking excitatory transmission.

Interestingly, acetazolamide is another carbonic anhydrase inhibitor that has been investigated in familial hemiplegic migraine and episodic ataxia type 2. Positive effects on ataxia have been observed with little or no prophylactic benefit for migraine.

Recent work suggests that topiramate may affect migraine through all of these ion channels and receptors. Studies have shown that each of the channel/receptor types are regulated by phosphorylation by protein kinase A and other kinases. Each of the channels/receptors shares a homologous amino acid sequence on the cytoplasmic side of the membrane-bound protein kinase A phosphorylation site, where protein kinase A catalyzes phosphorylation and the resulting cellular activation. It is thought that topiramate may bind at the protein kinase A phosphorylation site to prevent cellular activation and neurotransmission or may bind at the site only in the dephosphorylated state.

**Study Design**

The study reported here was a randomized, double-blind, placebo-controlled, parallel-group study of 213 patients with migraine, as defined by the International Headache Society, to assess the efficacy of topiramate. Randomization was 2:1 (topiramate:placebo). After a screening washout period of up to 28 days and a 28-day baseline period, participants were treated for 20 weeks with the study drug: an 8-week titration followed by 12 weeks of maintenance. The target dose of topiramate was 200 mg after an initial starting dose of 25 mg, with 25-mg increments weekly.

Of the 213 patients who were randomized, 140 were in the topiramate group and 73 were in the placebo group. At the end of the 20-week treatment period, 95 (68%) remained in the topiramate group and 60 (82%) remained in the placebo group. The reasons for discontinuation were similar between both groups and included lack of efficacy and protocol violation. Discontinuations were higher in the topiramate group for patient choice (6% vs 1%), adverse event (15% vs 5%), and loss to follow-up.

**Table 1. Topiramate Mechanisms of Action**

<table>
<thead>
<tr>
<th>Site</th>
<th>Action</th>
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<tbody>
<tr>
<td>Voltage-activated Na+ channels</td>
<td>Limits sustained repetitive firing via state-dependent blockade of Na+ channels</td>
</tr>
<tr>
<td>Ca++ channel subtypes</td>
<td>Reduces slightly the amplitude of high voltage-activated Ca++ currents</td>
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<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; receptor subtype(s)</td>
<td>Potentiates GABA-mediated inhibition at GABA&lt;sub&gt;A&lt;/sub&gt; site not modulated by benzodiazepines or barbiturates</td>
</tr>
<tr>
<td>Glutamate receptor subtypes (kainate and AMPA)</td>
<td>Blocks glutamate-mediated neuroexcitation with no apparent effect on NMDA receptor activity</td>
</tr>
<tr>
<td>Carbonic anhydrase</td>
<td>Inhibits type II and type IV carbonic anhydrase</td>
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</tbody>
</table>

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; Ca++ = calcium ion; GABA<sub>A</sub> = gamma-aminobutyric acid type A; Na+ = sodium ion; NMDA = N-methyl-D-aspartate.
(6% vs 0%). In the placebo group, discontinuations were higher than the topiramate group for reasons given as “other” (5% vs 1%).

Most of the patients in both groups achieved the target dose of 200 mg (61.3% topiramate, 86.4% placebo). The second most common dose for topiramate was 100 mg (12.3%), followed by 75 mg (9.4%). The mean dose of topiramate was 161.3 mg; for placebo, the mean dose was 185.6 mg, clearly indicating a placebo response.

**RESULTS**

The migraine frequency by month in the intention-to-treat population declined significantly during the first 2 months in both groups, from about 5 migraines per month to about 3.5 migraines per month. By month 3, the benefit reached a plateau for the placebo group; the topiramate group continued the decrease in monthly migraine frequency, but at a lower rate. The migraine frequency in the intention-to-treat populations did not significantly change overall (–1.04 placebo, –1.43 topiramate; *P* = .29). However, patients completing the study showed a significant change in overall migraine frequency between the 2 treatment groups (Figure).

Interestingly, there was no significant difference in the 50% response for both groups in the intention-to-treat population, again suggesting a placebo effect. However, significant differences in responder rates were observed for those patients achieving a 75% response or better (Table 2).

Of particular note, patients experiencing migraine with aura had the greatest benefit with topiramate treatment. The migraine frequency reduction was –2.43 vs –0.79 for the topiramate and placebo groups (intention-to-treat), respectively (*P* = .02).

All adverse events were greater in the topiramate group, with ranges of 2-fold to 10-fold differences. The most common adverse event with topiramate was paresthesias; for placebo, it was dizziness. A total of 14% of patients in the topiramate group experienced weight loss and nausea compared with 8% in the placebo group.

**CONCLUSION**

These results support other studies showing that topiramate is safe and effective for migraine prophylaxis. No serious adverse events were reported, and most interesting is the particular efficacy for patients suffering from migraine with aura.

**REFERENCES**


